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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/570,122

02/28/2006

Christine Power

ARS-122

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09/02/2008

SALIWANCHIK LLOYD & SALIWANCHIK

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EXAMINER

DEBERRY, REGINA M

ART UNIT

PAPER NUMBER

1647

MAIL DATE

DELIVERY MODE

09/02/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/570,122

Applicant(s)

POWER ET AL.

Examiner

Regina M. DeBerry

Art Unit

1647

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 46-59 is/are pending in the application.
- 4a) Of the above claim(s) 54 and 56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 45-53, 55 and 57-59 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 February 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10/06
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Status of Application, Amendments and/or Claims

The amendments, filed 28 February 2006 and 07 May 2008, have been entered in full. Claims 1-45 were canceled. New claims 45-59 were added. Applicant's election without traverse of Group II (claims 25-32, 36, 37 and 43) and species election of SEQ ID NO:2, in the reply filed on 07 May 2008 is acknowledged. Applicant states that by way of the amendment (07 May 2008), claims 46-59 have been added and that support for the new claims may be found in previously presented claims 25-45.

Claims 54 and 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group (or species), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07 May 2008. Claims 45-53, 55, 57-59 are under examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The certified copy has been filed in the instant application.

Information Disclosure Statement

The WO references listed on the information disclosure statement(s) (IDS), filed 24 October 2006, were not received and cannot be considered at this time. The other

references (database file registries) have been placed in the application file and the information referred to therein has been considered as to the merits.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application. Rule 37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01.

The specification refers to sequences on page 18, line 16; page 30, lines 1-4 and page 30, line 22, but does not identify the sequences by their sequence identifiers. The entire specification must be examined for proper sequence identifiers. Sequences appearing in drawings should be referenced in the corresponding Brief Description thereof. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (page 15, line 1). The specification should be reviewed for improper recitation of hyperlinks. All such recitations should be deleted or amended such that the hyperlinks and/or other form of browser-executable code are rendered inactive. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-53, 55, 57-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification states that the present invention is in the field of fibrotic diseases/connective tissue disorders and the use of INSP035 for the treatment and/or prevention of fibrotic diseases (page 1, lines 3-10). The specification teaches the full length cDNA of human INSP035 as SEQ ID NO:1 and the corresponding amino acid sequence as SEQ ID NO:2 (page 9, lines 23-26). The specification states that the invention is based on the finding that INSP035 is a potent inhibitor of TRAIL in an *in vitro* assay designed to select anti-apoptotic molecules in fibroblasts with osteoprotegerin (OPG) as control. The specification states that like OPG, INSP035 is able to counteract the apoptotic effect of soluble human recombinant TRAIL on fibroblast, thereby consistently reducing fibroblasts' apoptosis (page 7, lines 1-6). The specification states that administered OPG resulted in significant amelioration of fibrosis in an established animal model of lung fibrosis. The specification states that on the basis that OPG and INSP035 share common functionalities and on the findings that TRAIL stimulates collagen production, INSP035 is suggested to be useful in the treatment of fibrosis. The specification proposes that INSP035, as a TRAIL inhibitor, might lower the amount of TGFb present in the cells, which in turn would reduce collagen synthesis known to be deleterious in the pathogenesis of fibrosis (page 8, lines 9-18).

The instant claims are not enabled because the specification fails to teach how to treat a fibrotic diseases comprising administering INSP035. The specification teaches that INSP035 inhibits TRAIL in an *in vitro* assay to select anti-apoptotic molecules in fibroblast (Figure 1; page 25, lines 22-31 and page 27, lines 4-16) and that INSP035 is in various human tissues as measured by RT-PCR (pages 32-33). However, it could

not be predicted that the cell culture data presented in the specification would be in any way correlative with therapeutic agents for *in vivo* treatment of fibrotic diseases. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light. In addition, Yamamoto (Yamamoto, Arch. Dermatol. Res. 297:333-344, 2006), teaches the use of scleroderma animal models to understand treatments for human scleroderma. The instant specification fails to teach the use of any animal model to discern the *in vivo* effect of administered INSP035 on fibrosis.

Lastly, the claims are not enabled for a polypeptide that has at least 90% identity to SEQ ID NO:2 (INSP035). The specification does not teach how to make and use any variant of INSP035. The disclosure provides no guidance as to which regions of the INSP035 protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. For example, the specification states that INSP035 was identified as a leptin (page 5, lines 10-21), but Figure 2 demonstrates that leptin did not affect TRAIL-mediated apoptosis,

like INSP035. It is extremely complex to predict protein structure from sequence data and in turn utilizing calculated structural determinations to ascertain functional aspects of the protein. It is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any modified polypeptide could be used in the same manner as the native exemplar. Such experimentation would be undue for one skilled in this art.

Due to the large quantity of experimentation necessary to generate the number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes that there are many differences between cultured cells and their counterparts *in vivo*, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 45-53, 55, 57-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is reminded of the revision to the Written Description Training Materials, created on March 25, 2008 to supersede and replace the 1999 training materials. For more information, please see www.uspto.gov/web/menu/written.pdf.

The claimed subject matter is not supported by an adequate written description because a representative number of species has not been described. The specification discloses only a single species (i.e. SEQ ID NO:2). The instant claims are directed to the genus of variants of SEQ ID NO:2 that comprise an amino acid sequence at least 90% identical to SEQ ID NO:2, treats a fibrotic disease and inhibits TNF-related apoptosis-inducing ligand/Apo2 ligand (TRAIL). The specification discloses the reduction to practice of one species within the claimed genus; specifically, the protein having the amino acid sequence of SEQ ID NO:2. The recitation of a polypeptide with at least 90% amino acid sequence identity to SEQ ID NO:2 represents a partial structure. That is, the claimed proteins share at least 90% of the structure of SEQ ID NO:2, while 10% of the structure can vary. There is no teaching in the specification regarding which 10% of the structure can be varied while retaining the claimed function. Further, there is no art-recognized correlation between any structure and the activity of treating a fibrotic disease and inhibiting TRAIL based on which those of ordinary skill in the art could predict which amino acids can vary from SEQ ID NO:2 without losing the claimed activity. The specification states that INSP035 was identified as a leptin, but leptin did not affect TRAIL-mediated apoptosis. Thus, there is no information about which amino

acids can vary from SEQ ID NO:2 in the claimed genus of proteins and still retain the activity. Although the disclosure of SEQ ID NO:2 combined with the knowledge in the art, would put one in possession of proteins that are at least 90% identical to SEQ ID NO:2, the level of skill and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing which of those proteins having at least 90% identity to SEQ ID NO:2 have the claimed activity. Based on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that the applicant was in possession of the claimed genus of proteins based on disclosure of the single species of SEQ ID NO:2.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45-53, 55, 57-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are drawn to a method for treating a fibrotic disease comprising administering to a patient in need thereof an effective amount of a composition comprising a pharmaceutical acceptable carrier and SEQ ID NO:2. The instant claims are indefinite because they fail to define **what effect** is required. Furthermore, the claims do not have a step that clearly relates back to the preamble. The claims must achieve the goal stated in the preamble.

Claim 59 is indefinite because it recites the limitation "the method according to claim 46, wherein a composition comprising an interferon is administered..". Claim 46 does not recite "interferon". There is insufficient antecedent basis for this limitation in claim 59.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 46-53 and 55 are rejected under 35 U.S.C. 102(e) as being anticipated by Mintz et al., United States Patent Application Publication US 2007/0083334 A1.

The instant claims recite the limitation, "in need thereof". The limitation, "in need thereof" encompasses any patient that would benefit from administering SEQ ID NO:2 for any reason. The instant claims, as written, are not limited to treating patients suffering from a fibrotic disease.

Mintz et al. teach a 163 amino acid polypeptide sequence that is 100% identical to SEQ ID NO:2. Please see Appendix A, Result # 3 and Mintz et al. (page 56). Mintz et

al. teach that purified proteins can be administered to a patient or immunized in a host animal to make antibodies (paragraphs 0313 and 0331)(**applies to claims 46, 47, 53 and 55**). Mintz et al. teach fusion proteins comprising the polypeptide sequence (paragraphs 0291, 0291-0295). Mintz et al. teach that fusion proteins containing an Fc region can be purified using a protein A column and that they have increased stability (e.g. a greater circulating half-life) *in vivo* (**applies to claims 49-52**). Mintz et al. teach that the protein can include those in which a glycosylated residue is added or deleted (paragraph 0323)(**applies to claim 48**). Mintz et al. teach pharmaceutical compositions comprising the protein, protein encoding sequence or antibodies directed against such protein (paragraphs 0496 and 0584). Mintz et al. teach that pharmaceutical compositions of the invention may also include a therapeutic agent such as interferon-beta (paragraphs 0587-0588)(**applies to claims 57-59**).

Claim Objections

Claims 46, 49-52 are objected to because of the following informalities: The instant claims are not limited to the elected invention. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/R. M. D./
Examiner, Art Unit 1647
8/25/08

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646